NDA 20-304/S-009

JUL 24 2000

Bayer Corporation Pharmaceutical Division
Attention: Gautam Shah, Ph.D.
400 Morgan Lane
West Haven, CT 065 16

Dear Dr. Shah:

Please refer to your supplemental new drug application dated February 23, 2000, received February 24, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trasylol® (aprotinin) Injection.

We acknowledge receipt of your submission dated April 6, 2000.

This "Changes Being Effected" supplemental new drug application provides for revisions to the CLINICAL TRIALS, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS sections of the package insert.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted February 23, 2000). Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR314.80 and 314.81.

If you have any questions, call Julieann Du Beau, Regulatory Health Project Manager, at (30 1) 827-73 10.

Sincerely,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

TRASYLOL®
(aprotinin injection)

PZ500155 2/00

Anaphylactic or anaphylactoid reactions are possible when Trasylol® is administered. Hypersensitivity reactions are rare in patients with no prior exposure to aprotinin. The risk of anaphylaxis is increased in patients who are re-exposed to aprotinin-containing products. The benefit of Trasylol® to patients undergoing primary CABG surgery should be weighed against the risk of anaphylaxis should a second exposure to aprotinin be required. (See WARNINGS and PRECAUTIONS).

DESCRIPTION

Trasylol® (aprotinin injection), $C_{284}H_{432}N_{84}O_{79}S_7$, is a natural proteinase inhibitor obtained from bovine lung. Aprotinin (molecular weight of 6512 daltons), consists of 58 amino acid residues that are arranged in a single polypeptide chain, cross-linked by three disulfide bridges. It is supplied as a clear, colorless, sterile isotonic solution for intravenous administration. Each milliliter contains 10,000 KIU (Kallikrein Inhibitor Units) (1.4 mg/mL) and 9 mg sodium chloride in water for injection. Hydrochloric acid and/or sodium hydroxide is used to adjust the pH to 4.5-6.5.

CLINICAL PHARMACOLOGY

Mechanism of Action: Aprotinin is a broad spectrum protease inhibitor which modulates the systemic inflammatory response (SIR) associated with cardiopulmonary bypass (CPB) surgery. SIR results in the interrelated activation of the hemostatic, fibrinolytic, cellular and humoral inflammatory systems. Aprotinin, through its inhibition of multiple mediators [e.g., kallikrein, plasmin] results in the attenuation of inflammatory responses, fibrinolysis, and thrombin generation.

Aprotinin inhibits pro-inflammatory cytokine release and maintains glycoprotein homeostasis. In platelets, aprotinin reduces glycoprotein loss (e.g., GpIb, GpIIb/IIIa), while in granulocytes it prevents the expression of pro-inflammatory adhesive glycoproteins (e.g., CD11b).

The effects of aprotinin use in CPB involves a reduction in inflammatory response which translates into a decreased need for allogeneic blood transfusions, reduced bleeding, and decreased mediastinal re-exploration for bleeding.

Pharmacokinetics: The studies comparing the pharmacokinetics of aprotinin in healthy volunteers, cardiac patients undergoing surgery with cardiopulmonary bypass, and women undergoing hysterectomy suggest linear pharmacokinetics over the dose range of 50,000 KIU to 2 million KIU. After intravenous (IV) injection, rapid distribution of aprotinin occurs into the total extracellular space, leading to a rapid initial decrease in plasma aprotinin concentration. Following this distribution phase, a plasma half-life of about 150 minutes is observed. At later time points, (i.e., beyond 5 hours after dosing) there is a terminal elimination phase with a half-life of about 10 hours.

Average steady state intraoperative plasma concentrations were 137 KIU/mL (n=10) after administration of the following dosage regimen: 1 million KIU IV loading dose, 1 million KIU into the pump prime volume, 250,000 KIU per hour of operation as continuous intravenous infusion (Regimen B). Average steady state intraoperative plasma concentrations were 250 KIU/mL in patients (n=20) treated with aprotinin during cardiac surgery by administration of Regimen A (exactly double Regimen B): 2 million KIU IV loading dose, 2 million KIU into the pump prime volume, 500,000 KIU per hour of operation as continuous intravenous infusion.

Following a single IV dose of radiolabelled aprotinin, approximately 25-40% of the radioactivity is excreted in the urine over 48 hours. After a 30 minute infusion of 1 million KIU, about 2% is excreted as unchanged drug. After a larger dose of 2 million KIU infused over 30 minutes, urinary excretion of unchanged aprotinin accounts for approximately 9% of the dose. Animal studies have shown that aprotinin is accumulated primarily in the kidney. Aprotinin, after being filtered by the glomeruli, is actively reabsorbed by the proximal tubules in which it is stored in phagolysosomes. Aprotinin is slowly degraded by lysosomal enzymes. The physiological renal handling of aprotinin is similar to that of other small proteins, e.g., insulin.

CLINICAL TRIALS

Repeat Coronary Artery Bypass Graft Patients:

Four placebo-controlled, double-blind studies of Trasylol® were conducted in the United States; of 540 randomized patients undergoing repeat coronary artery bypass graft (CABG) surgery, 480 were valid for efficacy analysis. The following treatment regimens were used in the studies:

Trasylol® Regimen A (2 million KIU IV loading dose, 2 million KIU into the pump prime volume, and 500,000 KIU per hour of surgery as a continuous intravenous infusion); Trasylol® Regimen B (1 million KIU IV loading dose, 1 million KIU into the pump prime volume, and 250,000 KIU per hour of surgery as a continuous intravenous infusion); a pump prime regimen (2 million KIU into the pump prime volume only); and a placebo regimen (normal saline). All patients valid for efficacy in the above studies were pooled by treatment regimen for analyses of efficacy.

In this pooled analysis, fewer patients receiving Trasylol®, either Regimen A or Regimen B, required any donor blood compared to the pump prime only or placebo regimens. The number of units of donor blood required by patients, the volume (milliliters) of donor blood transfused, the number of units of donor blood products transfused, the thoracic drainage rate, and the total thoracic drainage volumes were also reduced in patients receiving Trasylol® as compared to placebo.

Efficacy Variables: Repeat CABG Patients
Mean (S.D.) or % of Patients

VARIABLE	PLACEBO REGIMEN N=156	Trasylol® PUMP PRIME REGIMEN† N=68	Trasylol® REGIMEN B** N=113	Trasylol® REGIMEN A** N=143
% OF REPEAT CABG PATIENTS WHO REQUIRED DONOR BLOOD	76.3%	72.1%	48.7%	46.9%
UNITS OF DONOR BLOOD TRANSFUSED	3.7 (4.4)	2.5 (2.4)	2.2 (5.0)*	1.6 (2.9)*
mL OF DONOR BLOOD TRANSFUSED	1132 (1443)	756 (807)	723 (1779)*	515 (999)*
PLATELETS TRANSFUSED (Donor Units)	5.0 (10.0)	2.1 (4.6)*	1.3 (4.6)*	0.9 (4.3)*
CRYOPRECIPITATE TRANSFUSED (Donor Units)	0.9 (3.5)	0.0 (0.0)*	0.5 (4.0)	0.1 (0.8)*
FRESH FROZEN PLASMA TRANSFUSED (Donor Units)	1.3 (2.5)	0.5 (1.4)*	0.3 (1.1)*	0.2 (0.9)*
THORACIC DRAINAGE RATE (mL/hr)	89 (77)	73 (69)	66 (244)	40 (36)*
TOTAL THORACIC DRAINAGE VOLUME (mL)[a]	1659 (1226)	1561 (1370)	1103 (2001)*	960 (849)*
REOPERATION FOR DIFFUSE BLEEDING	1.9%	2.9%	0%	0%

† The pump prime regimen was evaluated in only one study in patients undergoing repeat CABG surgery. Note: The pump prime only regimen is not an approved dosage regimen.

* Significantly different from placebo, $p<0.05$
(Transfusion variables analyzed via ANOVA on ranks)

** Differences between Regimen A (high dose) and Regimen B (low dose) in efficacy and safety are not statistically significant.

[a] Excludes patients who required reoperation

Primary Coronary Artery Bypass Graft Patients:

Four placebo-controlled, double-blind studies of Trasylol® were conducted in the United States; of 1745 randomized patients undergoing primary CABG surgery, 1599 were valid for efficacy analysis. The dosage regimens used in these studies were identical to those used in the repeat CABG studies described above (Regimens A, B, pump prime, and placebo). All patients valid for efficacy were pooled by treatment regimen.

In this pooled analysis, fewer patients receiving Trasylol® Regimens A, B, and pump prime required any donor blood in comparison to the placebo regimen. The number of units of donor blood required by patients, the volume of donor blood transfused, the number of units of donor blood products transfused, the thoracic drainage rate, and total thoracic drainage volumes were also reduced in patients receiving Trasylol® as compared to placebo.

Efficacy Variables: Primary CABG Patients
Mean (S.D.) or % of Patients

VARIABLE	PLACEBO REGIMEN N=624	Trasylol® PUMP PRIME REGIMEN† N=159	Trasylol® REGIMEN B** N=175	Trasylol® REGIMEN A** N=641
% OF PRIMARY CABG PATIENTS WHO REQUIRED DONOR BLOOD	53.5%	32.7%*	37.1%*	36.8%*
UNITS OF DONOR BLOOD TRANSFUSED	1.7 (2.4)	0.9 (1.6)*	1.0 (1.6)*	0.9 (1.4)*
mL OF DONOR BLOOD TRANSFUSED	584 (840)	286 (518)*	313 (505)*	295 (503)*
PLATELETS TRANSFUSED (Donor Units)	1.3 (3.7)	0.5 (2.4)*	0.3 (1.6)*	0.3 (1.5)*
CRYOPRECIPITATE TRANSFUSED (Donor Units)	0.5 (2.2)	0.0 (0.0)*	0.1 (0.8)*	0.0 (0.0)*
FRESH FROZEN PLASMA TRANSFUSED (Donor Units)	0.6 (1.7)	0.2 (1.7)*	0.2 (0.8)*	0.2 (0.9)*
THORACIC DRAINAGE RATE (mL/hr)	87 (67)	51 (36)*	45 (31)*	39 (32)*
TOTAL THORACIC DRAINAGE VOLUME (mL)	1232 (711)	852 (653)*	792 (465)*	705 (493)*
REOPERATION FOR DIFFUSE BLEEDING	1.4%	0.6%	0%	0%*

† The pump prime regimen was evaluated in only one study in patients undergoing primary CABG surgery. Note: The pump prime only regimen is not an approved dosage regimen.

* Significantly different from placebo, $p<0.05$
(Transfusion variables analyzed via ANOVA on ranks)

** Differences between Regimen A (high dose) and Regimen B (low dose) in efficacy and safety are not statistically significant.

Additional subgroup analyses showed no diminution in benefit with increasing age. Male and female patients benefited from Trasylol® with a reduction in the average number of units of donor blood transfused. Although male patients did better than female patients in terms of the percentage of patients who required any donor blood transfusions, the number of female patients studied was small.

A double-blind, randomized, Canadian study compared Trasylol® Regimen A (n=28) and placebo (n=23) in primary cardiac surgery patients (mainly CABG) requiring cardiopulmonary bypass who were treated with aspirin within 48 hours of surgery. The mean total blood loss (1209.7 mL vs. 2532.3 mL) and the mean number of units of packed red blood cells transfused (1.6 units vs 4.3 units) were significantly less ($p<0.008$) in the Trasylol® group compared to the placebo group.

In a U.S. randomized study of Trasylol® Regimen A and Regimen B versus the placebo regimen in 212 patients undergoing primary aortic and/or mitral valve replacement or repair, no benefit was found for Trasylol® in terms of the need for transfusion or the number of units of blood required.

INDICATIONS AND USAGE

Trasylol is indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery.

CONTRAINDICATIONS

Hypersensitivity to aprotinin.

WARNINGS

Anaphylactic or anaphylactoid reactions are possible when Trasylol® is administered. Hypersensitivity reactions are rare in patients with no prior exposure to aprotinin. Hypersensitivity reactions can range from skin eruptions, itching, dyspnea, nausea and tachycardia to fatal anaphylactic shock with circulatory failure. If a hypersensitivity reaction occurs during injection or infusion of Trasylol®, administration should be stopped immediately and emergency treatment should be initiated. It should be noted that severe (fatal) hypersensitivity/anaphylactic reactions can also occur in connection with application of the test dose. Even when a second exposure to aprotinin has been tolerated without symptoms, a subsequent administration may result in severe hypersensitivity/anaphylactic reactions.

Re-exposure to aprotinin: In a retrospective review of 387 European patient records with documented re-exposure to Trasylol®, the incidence of hypersensitivity/anaphylactic reactions was 2.7%. Two patients who experienced hypersensitivity/anaphylactic reactions subsequently died, 24 hours and 5 days after surgery, respectively. The relationship of these 2 deaths to Trasylol® is unclear. This retrospective review also showed that the incidence of a hypersensitivity or anaphylactic reaction following re-exposure is increased when the re-exposure occurs within 6 months of the initial administration (5.0% for re-exposure within 6 months and 0.9% for re-exposure greater than 6 months). Other smaller studies have shown that in case of re-exposure, the incidence of hypersensitivity/anaphylactic reactions may reach the five percent level.

Before initiating treatment with Trasylol® in a patient with a history of prior exposure to aprotinin or products containing aprotinin, the recommendations below should be followed to manage a potential hypersensitivity or anaphylactic reaction: 1) Have standard emergency treatments for hypersensitivity or anaphylactic reactions readily available in the operating room (e.g., epinephrine, corticosteroids). 2) Administration of the test dose and loading dose should be done only when the conditions for rapid cannulation (if necessary) are present. 3) Delay the addition of Trasylol® into the pump prime solution until after the loading dose has been safely administered. Additionally, administration of H1 and H2 blockers 15 minutes before the test dose may be considered.

PRECAUTIONS

General: *Test Dose:* All patients treated with Trasylol® should first receive a test dose to assess the potential for allergic reactions. The test dose of 1 mL Trasylol® should be administered intravenously at least 10 minutes prior to the loading dose. However, even after the uneventful administration of the initial 1 mL test-dose, the therapeutic dose may cause an anaphylactic reaction. If this happens the infusion of aprotinin should immediately be stopped, and standard emergency treatment for anaphylaxis be applied. It should be noted that hypersensitivity/anaphylactic reactions can also occur in connection with application of the test-dose. (see WARNINGS)

Allergic Reactions: Patients with a history of allergic reactions to drugs or other agents may be at greater risk of developing a hypersensitivity or anaphylactic reaction upon exposure to Trasylol®. (see WARNINGS)

Loading Dose: The loading dose of Trasylol® should be given intravenously to patients in the supine position over a 20-30 minute period. Rapid intravenous administration of Trasylol® can cause a transient fall in blood pressure. (see DOSAGE AND ADMINISTRATION).

Use of Trasylol® in patients undergoing deep hypothermic circulatory arrest: Two U.S. case control studies have reported contradictory results in patients receiving Trasylol® while undergoing deep hypothermic circulatory arrest in connection with surgery of the aortic arch. The first study showed an increase in both renal failure and mortality compared to age-matched historical controls. Similar results were not observed, however, in a second case control study. The strength of this association is uncertain because there are no data from randomized studies to confirm or refute these findings.

Drug Interactions: Trasylol® is known to have antifibrinolytic activity and, therefore, may inhibit the effects of fibrinolytic agents.

In study of nine patients with untreated hypertension, Trasylol® infused intravenously in a dose of 2 million KIU over two hours blocked the acute hypotensive effect of 100mg of captopril.

Trasylol®, in the presence of heparin, has been found to prolong the activated clotting time (ACT) as measured by a celite surface activation method. The kaolin activated clotting time appears to be much less affected. However, Trasylol® should not be viewed as a heparin sparing agent. (see Laboratory Monitoring of Anticoagulation During Cardiopulmonary Bypass).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies to evaluate the carcinogenic potential of Trasylol® or studies to determine the effect of Trasylol® on fertility have not been performed.

Results of microbial *in vitro* tests using *Salmonella typhimurium* and *Bacillus subtilis* indicate that Trasylol® is not a mutagen.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats at intravenous doses up to 200,000 KIU/kg/day for 11 days, and in rabbits at intravenous doses up to 100,000 KIU/kg/day for 13 days, 2.4 and 1.2 times the human dose on a mg/kg basis and 0.37 and 0.36 times the human mg/m^2 dose. They have revealed no evidence of impaired fertility or harm to the fetus due to Trasylol®. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mother: Not applicable.

Pediatric Use: Safety and effectiveness in pediatric patient(s) have not been established.

Geriatric Use: Of the total of 3083 subjects in clinical studies of Trasylol®, 1100 (35.7 percent) were 65 and over, while 297 (9.6 percent) were 75 and over. Of patients 65 years and older, 479 (43.5 percent) received Regimen A and 237 (21.5 percent) received Regimen B. No overall differences in safety or effectiveness were observed between these subjects and younger subjects for either dose regimen, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Laboratory Monitoring of Anticoagulation during Cardiopulmonary Bypass: Trasylol® prolongs whole blood clotting times by a different mechanism than heparin. In the presence of aprotinin, prolongation is dependent on the type of whole blood clotting test employed. If an

activated clotting time (ACT) is used to determine the effectiveness of heparin anticoagulation, the prolongation of the ACT by aprotinin may lead to an overestimation of the degree of anticoagulation, thereby leading to inadequate anticoagulation. During extended extracorporeal circulation, patients may require additional heparin, even in the presence of ACT levels that appear adequate.

In patients undergoing CPB with Trasylol® therapy, one of the following methods may be employed to maintain adequate anticoagulation:

1) ACT - An ACT is not a standardized coagulation test, and different formulations of the assay are affected differently by the presence of aprotinin. The test is further influenced by variable dilution effects and the temperature experienced during cardiopulmonary bypass. It has been observed that Kaolin-based ACTs are not increased to the same degree by aprotinin as are diatomaceous earth-based (celite) ACTs. While protocols vary, a minimal celite ACT of 750 seconds or kaolin-ACT of 480 seconds, independent of the effects of hemodilution and hypothermia, is recommended in the presence of aprotinin. Consult the manufacturer of the ACT test regarding the interpretation of the assay in the presence of Trasylol®.

2) Fixed Heparin Dosing - A standard loading dose of heparin, administered prior to cannulation of the heart, plus the quantity of heparin added to the prime volume of the CPB circuit, should total at least 350 IU/kg. Additional heparin should be administered in a fixed-dose regimen based on patient weight and duration of CPB.

3) Heparin Titration - Protamine titration, a method that is not affected by aprotinin, can be used to measure heparin levels. A heparin dose response, assessed by protamine titration, should be performed prior to administration of aprotinin to determine the heparin loading dose. Additional heparin should be administered on the basis of heparin levels measured by protamine titration. Heparin levels during bypass should not be allowed to drop below 2.7 U/mL (2.0 mg/kg) or below the level indicated by heparin dose response testing performed prior to administration of aprotinin.

Protamine Administration - In patients treated with Trasylol®, the amount of protamine administered to reverse heparin activity should be based on the actual amount of heparin administered, and not on the ACT values.

ADVERSE REACTIONS

Studies of patients undergoing CABG surgery, either primary or repeat, indicate that Trasylol® is generally well tolerated. The adverse events reported are frequent sequelae of cardiac surgery and are not necessarily attributable to Trasylol® therapy. Adverse events reported, up to the time of hospital discharge, from patients in US placebo-controlled trials are listed in the following table. The table lists only those events that were reported in 2% or more of the Trasylol® treated patients without regard to causal relationship.

INCIDENCE RATES OF ADVERSE EVENTS (> = 2%) BY BODY SYSTEM AND TREATMENT FOR ALL PATIENTS FROM US PLACEBO-CONTROLLED CLINICAL TRIALS

Adverse Event	Aprotinin (n = 2002) values in %	Placebo (n = 1084) values in %
Any Event	76	77
Body as a Whole		
Fever	15	14
Infection	6	7
Chest Pain	2	2
Asthenia	2	2
Cardiovascular		
Atrial Fibrillation	21	23
Hypotension	8	10
Myocardial Infarct	6	6
Atrial Flutter	6	5
Ventricular Extrasystoles	6	4
Tachycardia	6	7
Ventricular Tachycardia	5	4
Heart Failure	5	4
Pericarditis	5	5
Peripheral Edema	5	5
Hypertension	4	5
Arrhythmia	4	3
Supraventricular Tachycardia	4	3
Atrial Arrhythmia	3	3
Digestive		
Nausea	11	9
Constipation	4	5
Vomiting	3	4
Diarrhea	3	2
Liver Function Tests Abnormal	3	2
Hemic and Lymphatic		
Anemia	2	8
Metabolic & Nutritional		
Creatine Phosphokinase Increased	2	1
Musculoskeletal		
Any Event	2	3
Nervous		
Confusion	4	4
Insomnia	3	4
Respiratory		
Lung Disorder	8	8
Pleural Effusion	7	9
Atelectasis	5	6
Dyspnea	4	4
Pneumothorax	4	4
Asthma	2	3
Hypoxia	2	1
Skin and Appendages		
Rash	2	2
Urogenital		
Kidney Function Abnormal	3	2
Urinary Retention	3	3
Urinary Tract Infection	2	2

In comparison to the placebo group, no increase in mortality in patients treated with Trasylol® was observed. Additional events of particular interest from controlled US trials with an incidence of less that 2%, are listed below:

EVENT	Percentage of patients treated with Trasylol N = 2002	Percentage of patients treated with Placebo N = 1084
Thrombosis	1.0	0.6
Shock	0.7	0.4
Cerebrovascular Accident	0.7	2.1
Thrombophlebitis	0.2	0.5
Deep Thrombophlebitis	0.7	1.0
Lung Edema	1.3	1.5
Pulmonary Embolus	0.3	0.6
Kidney Failure	1.0	0.6
Acute Kidney Failure	0.5	0.6
Kidney Tubular Necrosis	0.8	0.4

Listed below are additional events, from controlled US trials with an incidence between 1 and 2%, and also from uncontrolled, compassionate use trials and spontaneous post-marketing reports. Estimates of frequency cannot be made for spontaneous post-marketing reports *(italicized)*.

Body as a Whole: Sepsis, death, multi-system organ failure, immune system disorder, *hemoperitoneum*.

Cardiovascular: Ventricular fibrillation, heart arrest, bradycardia, congestive heart failure, hemorrhage, bundle branch block, myocardial ischemia, ventricular tachycardia, heart block, pericardial effusion, ventricular arrhythmia, shock, pulmonary hypertension.

Digestive: Dyspepsia, gastrointestinal hemorrhage, jaundice, hepatic failure.

Hematologic and Lymphatic: Although thrombosis was not reported more frequently in aprotinin versus placebo-treated patients in controlled trials, it has been reported in uncontrolled trials, compassionate use trials, and spontaneous post-marketing reporting. These reports of thrombosis encompass the following terms: thrombosis, occlusion, arterial thrombosis, *pulmonary thrombosis*, coronary occlusion, embolus, pulmonary embolus, thrombophlebitis, deep thrombophlebitis, cerebrovascular accident, cerebral embolism. Other hematologic events reported include leukocytosis, thrombocytopenia, coagulation disorder (which includes disseminated intravascular coagulation), decreased prothombin.

Metabolic and Nutritional: Hyperglycemia, hypokalemia, hypervolemia, acidosis.

Musculoskeletal: Arthralgia.

Nervous: Agitation, dizziness, anxiety, convulsion.

Respiratory: Pneumonia, apnea, increased cough, lung edema.

Skin: *Skin discoloration*.

Urogenital: Oliguria, kidney failure, acute kidney failure, kidney tubular necrosis.

Myocardial Infarction: In the pooled analysis of all patients undergoing CABG surgery, there was no significant difference in the incidence of investigator-reported myocardial infarction (MI) in Trasylol® treated patients as compared to placebo treated patients. However, because no uniform criteria for the diagnosis of myocardial infarction were utilized by investigators, this issue was addressed prospectively in three later studies (two studies evaluated Regimen A, Regimen B and Pump Prime Regimen; one study evaluated only Regimen A), in which data were analyzed by a blinded consultant employing an algorithm for possible, probable or definite MI. Utilizing this method, the incidence of definite myocardial infarction was 5.9% in the aprotinin-treated patients versus 4.7% in the placebo treated patients. This difference in the incidence rates was not statistically significant. Data from these three studies are summarized below.

Incidence of Myocardial Infarctions by Treatment Group Population: All CABG Patients Valid for Safety Anaylsis

Treatment	Definite MI %	Definite or Probable MI %	Definite, Probable or Possible MI %
Pooled Data from Three Studies that Evaluated Regimen A			
Trasylol® Regimen A n = 646	4.6	10.7	14.1
Placebo n = 661	4.7	11.3	13.4
Pooled Data from Two Studies that Evaluated Regimen B and Pump Prime Regimen			
Trasylol® Regimen B n = 241	8.7	15.9	18.7
Trasylol® Pump Prime Regimen n = 239	6.3	15.7	18.1
Placebo n = 240	6.3	15.1	15.8

Graft Patency: In a recently completed multi-center, multi-national study to determine the effects of Trasylol® Regimen A vs. placebo on saphenous vein graft patency in patients undergoing primary CABG surgery, patients were subjected to routine postoperative angiography. Of the 13 study sites, 10 were in the United States and three were non-U.S. centers (Denmark (1), Israel (2)). The results of this study are summarized below.

Incidence of Graft Closure, Myocardial Infarction and Death by Treatment Group

	Overall Closure Rates*		Incidence of MI**	Incidence of Death***
	All Centers n = 703 %	U.S. Centers n = 381 %	All Centers n = 831 %	All Centers n = 870 %
Trasylol®	15.4	9.4	2.9	1.4
Placebo	10.9	9.5	3.8	1.6
CI for the Difference (%) (Drug - Placebo)	(1.3, 9.6)†	(-3.8, 5.9)†	-3.3 to 1.5‡	-1.9 to 1.4‡

* Population: all patients with assessable saphenous vein grafts
** Population: all patients assessable by blinded consultant
*** All patients
† 90%; per protocol
‡ 95%; not specified in protocol

Although there was a statistically significantly increased risk of graft closure for Trasylol® treated patients compared to patients who received placebo (p=0.035), further analysis showed a significant treatment by site interaction for one of the non-U.S. sites vs. the U.S. centers. When the analysis of graft closures was repeated for U.S. centers only, there was no statistically significant difference in graft closure rates in patients who received Trasylol® vs. placebo. These results are the same whether analyzed as the proportion of patients who experienced at least one graft closure postoperatively or as the proportion of grafts closed. There were no differences between treatment groups in the incidence of myocardial infarction as evaluated by the blinded consultant (2.9% Trasylol® vs. 3.8% placebo) or of death (1.4% Trasylol® vs. 1.6% placebo) in this study.

Hypersensitivity and Anaphylaxis: See WARNINGS.

Hypersensitivity and anaphylactic reactions during surgery were rarely reported in U.S. controlled clinical studies in patients with no prior exposure to Trasylol® (1/1424 patients or <0.1% on Trasylol® vs. 1/861 patients or 0.1% on placebo). In case of re-exposure the incidence of hypersensitivity/anaphylactic reactions has been reported to reach the 5% level. A review of 387 European patient records involving re-exposure to Trasylol® showed that the incidence of hypersensitivity or anaphylactic reactions was 5.0% for re-exposure within 6 months and 0.9% for re-exposure greater than 6 months.

Laboratory Findings

Serum Creatinine: Data pooled from all patients undergoing CABG surgery in U.S. placebo-controlled trials showed no statistically or clinically significant increase in the incidence of postoperative renal dysfunction in patients treated with Trasylol®. The incidence of serum creatinine elevations > 0.5 mg/dL above pre-treatment levels was 9% in the Trasylol® group vs. 8% in the placebo group (p=0.248), while the incidence of elevations >2.0 mg/dL above baseline was only 1% in each group (p=0.883). In the majority of instances, postoperative renal dysfunction was not severe and was reversible. Patients with baseline elevations in serum creatinine were not at increased risk of developing postoperative renal dysfunction following Trasylol® treatment.

Serum Transaminases: Data pooled from all patients undergoing CABG surgery in U.S. placebo-controlled trials showed no evidence of an increase in the incidence of post-operative hepatic dysfunction in patients treated with Trasylol®. The incidence of treatment-emergent increases in ALT (formerly SGPT) > 1.8 times the upper limit of normal was 14% in both the Trasylol® and placebo-treated patients (p=0.687), while the incidence of increases > 3 times the upper limit of normal was 5% in both groups (p=0.847).

Other Laboratory Findings: The incidence of treatment-emergent elevations in plasma glucose, AST (formerly SGOT), LDH, alkaline phosphatase, and CPK-MB was not notably different between Trasylol® and placebo treated patients undergoing CABG surgery. Significant elevations in the partial thromboplastin time (PTT) and celite Activated Clotting Time (celite ACT) are expected in Trasylol® treated patients in the hours after surgery due to circulating concentrations of Trasylol®, which are known to inhibit activation of the intrinsic clotting system by contact with a foreign material (e.g., celite), a method used in these tests. (see Laboratory Monitoring of Anticoagulation During Cardiopulmonary Bypass).

OVERDOSAGE

The maximum amount of Trasylol® that can be safely administered in single or multiple doses has not been determined. Doses up to 17.5 million KIU have been administered within a 24 hour period without any apparent toxicity. There is one poorly documented case, however, of a patient who received a large, but not well determined, amount of Trasylol® (in excess of 15 million KIU) in 24 hours. The patient, who had pre-existing liver dysfunction, developed hepatic and renal failure postoperatively and died. Autopsy showed hepatic necrosis and extensive renal tubular and glomerular necrosis. The relationship of these findings to Trasylol® therapy is unclear.

DOSAGE AND ADMINISTRATION

Trasylol® given prophylactically in both Regimen A and Regimen B (half Regimen A) to patients undergoing CABG surgery significantly reduced the donor blood transfusion requirement relative to placebo treatment. In low risk patients there is no difference in efficacy between regimen A and B. Therefore, the dosage used (A vs. B) is at the discretion of the practitioner.

Trasylol® is supplied as a solution containing 10,000 KIU/mL, which is equal to 1.4 mg/mL. All intravenous doses of Trasylol® should be administered through a central line. **DO NOT ADMINISTER ANY OTHER DRUG USING THE SAME LINE.** Both regimens include a 1 mL test dose, a loading dose, a dose to be added while **recirculating** the priming fluid of the cardiopulmonary bypass circuit ("pump prime" dose), and a constant infusion dose. To avoid physical incompatibility of Trasylol® and heparin when adding to the pump prime solution, each agent must be added **during recirculation** of the pump prime to assure adequate dilution prior to admixture with the other component. Regimens A and B (both incorporating a 1 mL test dose) are described in the table below:

	TEST DOSE	LOADING DOSE	"PUMP PRIME" DOSE	CONSTANT INFUSION DOSE
TRASYLOL® REGIMEN A	1 mL (1.4 mg, or 10,000 KIU)	200 mL (280 mg, or 2.0 million KIU)	200 mL (280 mg, or 2.0 million KIU)	50 mL/hr (70 mg/hr, or 500,000 KIU/hr)
TRASYLOL® REGIMEN B	1 mL (1.4 mg, or 10,000 KIU)	100 mL (140 mg, or 1.0 million KIU)	100 mL (140 mg, or 1.0 million KIU)	25 mL/hr (35 mg/hr, or 250,000 KIU/hr)

The 1 mL test dose should be administered intravenously at least 10 minutes before the loading dose. With the patient in a supine position, the loading dose is given slowly over 20-30 minutes, after induction of anesthesia but prior to sternotomy. In patients with known previous exposure to Trasylol®, the loading dose should be given just prior to cannulation. When the loading dose is complete, it is followed by the constant infusion dose, which is continued until surgery is complete and the patient leaves the operating room. The "pump prime" dose is added to the **recirculating** priming fluid of the cardiopulmonary bypass circuit, by replacement of an aliquot of the priming fluid, prior to the institution of cardiopulmonary bypass. Total doses of more than 7 million KIU have not been studied in controlled trials.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Discard any unused portion.

Renal and Hepatic Impairment: No formal studies of the pharmacokinetics of aprotinin in patients with pre-existing renal insufficiency have been conducted. However, in the placebo-controlled clinical trials conducted in the United States, patients with mildly elevated pre-treatment serum creatinine levels did not have a notably higher incidence of clinically significant post-treatment elevations in serum creatinine following either Trasylol® Regimen A or Regimen B compared to administration of the placebo regimen. Changes in aprotinin pharmacokinetics with age or impaired renal function are not great enough to require any dose adjustment. No pharmacokinetic data from patients with pre-existing hepatic disease treated with Trasylol® are available.

HOW SUPPLIED

Size	Strength	NDC
100 mL vials	1,000,000 KIU	0026-8196-36
200 mL vials	2,000,000 KIU	0026-8197-63

STORAGE

Trasylol® should be stored between 2° and 25°C (36° - 77°F).

Protect from freezing.

Bayer Corporation
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Made in Germany

℞ **Only**

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